REMARKS

With this response, claims 24-30 and 38-59 are pending. Claims 24-26, 28, and 56 have been amended without prejudice or disclaimer, and claims 31-37 and 60-69 have been canceled without prejudice or disclaimer by way of the present amendment. It is noted that claims 31-37 and 60-69 have been canceled as directed to a non-elected invention. Regardless, Applicants reserve the right to prosecute the non-elected invention in a continuing application. Support for the foregoing amendment can be found throughout the specification and the claims as originally filed, for example, in the Substitute Specification at page 13, line 24 through page 14, line 10; and page 29, lines 6-19.

I. Information Disclosure Statement

Applicants thank the Examiner for the Examiner-initialed copy of the PTO-1449 forms submitted by Applicants on February 19, 2004.

II. Objection to the Specification

The specification has been objected to as allegedly having "improperly" incorporated by reference amylin agonist analogs disclosed in WPI 182488, which corresponds to WO 9310146. Applicants had amended the specification by a Preliminary Amendment on August 18, 2003. Accordingly, this objection is respectfully traversed. Nonetheless, in order to facilitate prosecution, a Substitute Specification is submitted herewith without prejudice under 37 C.F.R. § 1.125. Pursuant to 37 C.F.R. § 1.125, a marked up version of the Substitute Specification showing all of the changes to the Specification of Record is attached. In addition, a marked up version of the Specification as filed is submitted showing the Preliminary Amendment on August 18, 2003 in bold. The Substitute Specification contains no new matter. In light of the above, Applicants believe this objection is moot and withdrawal of this objection is requested.

III. Sequence Rules

A Substitute Sequence Listing is provided in conjunction with the Substitute Specification.

IV. Rejection under 35 U.S.C. § 112, First Paragraph, Written Description

Claims 25-30 and 41-59 stand rejected under 35 U.S.C. §112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *Id.* at page 4.

New Matter Rejection

The Examiner argues the presently claimed subgenus of amylin agonist analogues as defined by the presently claimed invention are not described in the specification. Additionally, with regard to claims 56-59, the Examiner further alleges that there is no support for the scope of amino acids encompassed by the proviso "then one or more of any of A_1 to M_1 is not an L-amino acid and Z is not amino." *Id.* Applicants respectfully disagree.

In order to facilitate prosecution, Applicants have enclosed a Substitute Specification, a marked up copy of the Substitute Specification indicating changes from the Specification of Record, and a marked up copy of the Specification as originally filed showing the Preliminary Amendment submitted on August 18, 2003 in bold. Specifically, the presently claimed subgenus of amylin agonist analogues are described, for example, in the Substitute Specification on page 16, line 27 through page 17, line 19. Support for the proviso "then one or more of any of A_1 to M_1 is not an L-amino acid and Z is not amino" is on page 17, lines 18-19 of the Substitute Specification. In light of filing this Substitute Specification, the rejection under 35 U.S.C. § 112, first paragraph is moot, and withdrawal of this rejection is respectfully requested.

Lack of Written Description Rejection

In support of this rejection, the Examiner alleges that "[n]o disclosure of particular receptors or specific functions are disclosed. Accordingly, the amylin analogue definition fails to define the types of derivations of amylin encompassed by the definition nor is there any defined limits with regard to function which is necessary to satisfy the amylin agonist analogue." Office Action at page 6. Applicants respectfully disagree.

The standard for determining whether a claim drawn to a genus meets the written description requirement is clear. "The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice . . . , reduction to drawings . . . , or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus." *See Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406; M.P.E.P § 2163(II)(3)(a)(ii) (emphasis added). A "representative number of species" means that the species which are adequately described are representative of the entire genus. Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces. *Id.*

The instant specification provides characteristics defining amylin agonists and amylin agonist analogues, including derivatives, for example, possessing activity as amylin agonist agents such as moderating the postprandial rise in plasma glucose in mammals. Moreover, the present application teaches how such activity can be measured such as by Examples 2-4 on pages 31-36 of the Substitute Specification. Assays for determining amylin activity also include a soleus muscle assay and a receptor binding assay, as described in the application. *See* Substitute Specification, for example, at page 21, line 3 through page 22, line 5; page 22, lines 6-31; and Examples 24 and 25 on pages 49-52. Other assays for verifying amylin activity are also known in the art. *See also* Applicants' International Application No. PCT/US92/09842, entitled "Amylin Agonist Peptides and Uses Therefor." As such, Applicants have fully supported the terms "amylin agonist" and "amylin agonist analogue."

The Examiner further alleges that "no structure limitation appears to limit what constitutes an 'amylin agonist.'" Office Action at page 6. Applicants respectfully disagree. Applicants have satisfied the written description requirement by describing a representative number of amylin agonists and amylin agonist analogues, *e.g.* $^{18}Arg^{25,28}Pro$-h-amylin, des-$^{1}Lys^{18}Arg^{25,28}Pro$-h-amylin, and others. The instant specification demonstrates that Applicants were in possession of the claimed genus of amylin analogs. The Examiner's attention is also

directed to Applicants' International Application No. PCT/US92/09842, entitled "Amylin Agonist Peptides and Uses Therefor," which describes agonist analogues of amylin.

Applicants have provided sufficient guidance and working examples as to structural and functional characterization of the claimed amylin agonists, *e.g.*, through extensive disclosure of amylin analog sequences, and/or assays for verifying amylin activity, such as reducing or moderating postprandial plasma glucose concentrations (also referred to as "smoothing"). Accordingly, Applicants submit that amylin agonists and agonist analogs, including derivatives, are sufficiently described in the specification to reasonably convey to one of ordinary skill in the art that the inventors, at the time the application was filed, had possession of the claimed invention.

The Examiner acknowledges that Applicants' specification discloses murine, canine and human species. Office Action at page 6. However, to support the rejection, the Examiner argues that Applicants are not in possession of claimed subject matter "directed to 'a subject' broadly encompass[ing] any animal possessing a GI tract." *Id.* Applicants respectfully submit that the disclosure of murine, canine and human species fairly represents the genus of mammals. These are species routinely used in the art to discover/uncover the effects of test compounds in mammals.

Applicants respectfully submit that one skilled in the art would readily appreciate that Applicants, at the time of the filing of the present application, were in possession of the claimed genus and, therefore, have met the written description requirement. As such, it is submitted that the amended claims comply with 35 U.S.C. §112, first paragraph, and withdrawal of this rejection is respectfully requested.

V. Rejection under 35 U.S.C. § 112, First Paragraph, Enablement

Claims 24 and 38-40 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly not enabling one of skill in the art to make and/or use the invention. The Examiner acknowledges that the specification is enabled for the use of amylin and specifically disclosed amylin analogues. Office Action at page 8. However, the Examiner asserts that the specification "does not reasonably provide enablement for the use of amylin agonists which differ from a[m]ylin agonist analogues as defined and exemplified in the specification." *Id.*

Applicants respectfully traverse this rejection. Initially, it is submitted that the Examiner has not met the evidentiary burden to impose an enablement rejection for failure to enable one of skill to use the invention. A specification that discloses how to make and use a claimed invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented "must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436, 1441 (Fed. Cir. 1995) (*quoting In re Marzocchi*, 439 F.2d 220, 223, 169 U.S.P.Q. 367, 369 (CCPA. 1971) (emphasis in original)).

Applicants have provided direction and guidance, and have presented numerous examples of amylin agonists such that it is well within the level of ordinary skill in the art to practice the invention without undue experimentation. Considerable direction and guidance about how to make and use amylin agonists are provided in the instant specification as well as in the art and in commonly owned applications disclosing amylin analogs. *See* Substitute Specification, for example, in Examples 2-5 and 7-25. The Examiner has not provided sufficient evidence to cast doubt on the guidance provided in the specification. The law provides that experimentation is not necessarily undue simply because it is complex, if the art typically engages in such experimentation. *See In re Certain Limited-Charge Cell Culture Microcarriers*, 221 U.S.P.Q. 1165, 1174, (Int'l Trade Comm'n 1983) *aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 U.S.P.Q. 428 (Fed. Cir. 1985).

For instance, based on the guidance provided in the art regarding assays for amylin activity, including activity in the receptor binding assay and in the soleus muscle assay, the additional therapeutically active amylin agonists and amylin agonist analogs can be identified without the need for undue experimentation. The Examiner's attention is respectfully drawn to the examples that provide guidance, particularly to a person of skill in the art. First, Example 2 establishes the ability of an amylin agonist to reduce postprandial hyperglycemia when administered to a mammal. Second, Example 3 illustrates that a gastrointestinal effect is responsible for the reduction in postprandial hyperglycemia. Third, Example 4 demonstrates a

postprandial smoothing effect on plasma glucose concentration. Based on such guidance, one of skill in the art would be able to practice the claimed invention with only routine experimentation.

Moreover, an analysis of the *In re Wands* criteria further supports Applicants' position that no undue experimentation would be required to make and use the claimed invention. *See In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1998). The first *Wands* criterion is the quantity of experimentation necessary. The "make-and-test" quantum of experimentation is reduced by the extensive knowledge provided by the Applicants or in the art to which a person of ordinary skill in the art has access, *e.g.*, various mechanisms for assaying amylin activity, and testing the effects of glucagonostatic agents of disease states characterized by elevated glucagon levels. Performing routine and well-known steps, such as activity assays, cannot create undue experimentation, even if it is laborious. *See In re Angstadt*, 537 F.2d 498, 504, 190 U.S.P.Q. 214, 218-219 (CCPA 1976). The specification expressly provides numerous suggestions of amylin agonists, which would be expected to be effective within the various therapeutic claimed regimens that are also disclosed in the specification.

The second and third *Wands* criteria relate to the amount of direction or guidance given, and the presence or absence of working examples. As discussed above, the instant specification discloses ample guidance and direction in the form of the identification of a representative number of specific amylin agonists and methodologies to prepare such amylin agonists as known in the art, provided for in Applicants' co-owned International Application No. PCT/US92/09842, entitled "Amylin Agonist Peptides and Uses Therefor," and provided for in working examples demonstrating the success of using an amylin agonist for treatment. The Examiner provides no basis for the conclusion that demonstration of efficacy with respect to a single amylin analogue regarding reducing or moderating a postprandial rise in plasma glucose is not commensurate in scope as compared with the scope of the claims. Applicants have provided numerous representative examples of amylin agonists and demonstrated a dose-dependent effect of such an amylin agonist in reduction of postprandial hyperglycemia.

The fourth, fifth, and sixth *Wands* criteria focus on the nature of the invention, the state of the art, and the relative skill in the art. The present invention relates to methods for reducing or moderating a postprandial rise in plasma glucose in a mammal comprising administering amylin

or an amylin agonist. Considerable knowledge and resources, particularly those provided by the Applicant, guide practitioners in this art as to the conditions and approaches that can be utilized to prepare and assay such compounds. Moreover, as discussed above, the present specification itself adds to the relative skill in the art by providing detailed guidance regarding the application of such techniques to the art of the present invention. Such resources, combined with the specification and the general knowledge of those skilled in the art provide ample guidance to enable one of ordinary skill in the art to make and use the claimed invention.

The seventh criterion considers the predictability of the art. The Examiner alleges that the claimed invention "the pharmacological and pharmacokinetic properties of amylin have not been extensively characterize[d], and are therefore difficult to predict," and that "substrate/receptor binding is unpredictable." Office Action at pages 9-10. The Examiner appears to rely on the concept that "minor changes in substrate structure may result in inactive substrate analogue." *Id.* at page 10. Even assuming, *arguendo*, that such a concept is accurate, determination of such procedures and protocols is well within the level of skill in the art. Further, it is submitted that the specification discloses sufficient guidance to render the results predictable within the context of the amylin agonists of the invention. In fact, by providing guidance as to the selection of amylin agonists and the demonstration of amylin activity, Applicants have enabled the claimed invention.

The eighth criterion focuses on the breadth of the claims. Enablement is satisfied when the disclosure "adequately guide[s] the art worker to determine, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed utility." *In re Vaeck,* 947 F.2d 488, 496, 20 U.S.P.Q.2d 1438, 1445 (Fed. Cir. 1991). In the present case, one of skill in the art is specifically guided by the disclosure to make specific changes in the amylin structure, and is provided sufficient methodology to prepare amylin agonists and to verify activity of such compounds. As such, based on the teachings of the specification, one of skill in the art would be able to ascertain which species possess the disclosed utility and thus fall within the scope of the claims. It is thus submitted that the specification provides enablement commensurate in scope with the claims.

Accordingly, for at least these reasons, it is submitted that the claims are sufficiently

enabled under 35 U.S.C. § 112, first paragraph, and withdrawal of this rejection is respectfully requested.

VI. Rejection under 35 U.S.C. § 112, Second Paragraph, Definiteness

Claims 24 and 38-40 stand rejected under 35 U.S.C. § 112 as allegedly indefinite in that the recitations "an amylin or amylin agonist" lacks metes and bounds as to what compounds will or will not infringe the claimed invention. This rejection is respectfully traversed. It is submitted that one of skill in the art would be apprised of the scope of the present claims.

More particularly, the Examiner asserts that the term "amylin agonist" is indefinite because "[t]he specification on page 22 broadly defines an 'amylin agonist' as 'compounds which mimic the effects of amylin' without disclos[ing] what effects are encompassed or what degree of mimicry is required in order to fit within the open-ended specification definition." Office Action at page 11. The law merely requires that "the claims read in light of the specification reasonably apprise those skilled in the art of the scope ...." *Credle v. Bond*, 25 F.3d 1566, 1576, 30 U.S.P.Q.2d 1911, 1919 (Fed. Cir. 1994) (emphasis added). The degree of precision need only be "as accurate as the subject matter permits." *See Orthokinectics, Inc. v. Safety Travel Chains, Inc.* 806 F.2d 1565, 1 U.S.P.Q.2d 1081, 1088 (Fed. Cir. 1986). The claims are directed to amylin and amylin agonists which can be provided in an amount effective to reduce or moderate postprandial plasma glucose. The specification provides at least Example 4, one exemplary assay for reducing or moderating postprandial plasma glucose. Accordingly, the term "amylin agonist" is not impermissibly indefinite. It is submitted that one of skill in the art will readily appreciate that "amylin agonist" refers to a compound that achieves an effect of reducing or moderating postprandial plasma glucose.

The Examiner further alleges that "the amylin analogue definition fails to define the types of derivations of amylin encompassed by the definition nor is there any defined limits [sic] regard to function which is necessary to satisfy the amylin agonist analogue." Office Action at page 11. Applicants disagree. Analogs of a molecule are structurally related to the molecule, while agonists are functionally related to the molecule. This distinction is well known in the art. The specification, including incorporated documents, makes clear that agonists may be a subset of analogs within the context of the invention. Moreover, preferred amylin agonist analogues are

listed in the specification. Further, multiple assays for amylin agonists as determined by amylin-like function are provided in the specification, incorporated documents, and are well known in the art. What's more, when read in the context of the claim as a whole, it is clear that the claimed amylin agonists are capable of being administered in therapeutic amounts such that postprandial rise in plasma glucose is reduced or moderated. As such, one of skill in the art would clearly comprehend that the presently claimed amylin agonists must exhibit an activity of reducing or moderating postprandial plasma glucose. It is thus submitted that the claim term "amylin agonist" is clear and definite, and withdrawal of this rejection is respectfully requested.

VII. Rejection under 35 U.S.C. § 102

U.S. Patent No. 6,136,820 to Liu *et al.*

Claims 24 and 38-40 stand rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 6,136,820 to Liu *et al.* ("Liu"). This rejection is respectfully traversed for at least the reasons which follow. Initially, it is submitted that Liu fails to teach, disclose or suggest amylin or an amylin agonist, much less suggest the ability of amylin or amylin agonists to reduce or moderate a postprandial rise in plasma glucose.

Nonetheless, in support of this rejection, the Examiner alleges that "Lui et al. [d]iscloses and claims treating diabetes ... and postprandial hyperglycemia in diabetic individuals ... by administering castanospermine (e.g. an 'amylin agonist')." Office Action at page 13.

The Examiner appears to conclude that any molecule that treats postprandial hyperglycemia is necessarily an amylin agonist. In fact, not all methods of treating postprandial hyperglycemia use an amylin agonist. For example, insulin is used to treat postprandial hyperglycemia by regulating glucose disposal in the circulation. However, it is known in the art that insulin is not an amylin agonist. Lui is another such case. Castanospermine inhibits intestinal glycosideases (i.e. maltase and sucrase). *See* Lui col. 1, lines 45-46. Castanospermine is not an amylin agonist. Applicants submit that a conclusion otherwise, as drawn by the Examiner here, finds no support in the cited art.

More particularly, inhibition of intestinal glycosideases and reducing a postprandial rise in plasma glucose are distinct functions. As such, one of skill in the art would not expect amylin

or amylin agonist activity to correlate to inhibition of intestinal glycosideases. For example, amylin does not stimulate insulin secretion, yet it is known to suppress glucagon. As such, stimulation of insulin secretion would not be amylin or amylin agonist activity even if glucagon were suppressed. All this points to the fact that one of skill in the art would not conclude that a moderation or reduction of postprandial rise in plasma glucose resulted from amylin or an amylin agonist, when such moderation or reduction is correlated with a non-amylin activity, *i.e.* inhibition of intestinal glycosideases. Castanospermine does not function like amylin, and therefore is not an amylin agonist. As such, it is submitted that one of skill in the art would recognize that castanospermine is not an amylin agonist.

In sum, whatever else Lui does teach, it does not disclose the presently claimed invention. For at least these reasons, it is respectfully submitted that Lui does not anticipate the present claims. Therefore, reconsideration and withdrawal of this rejection is respectfully requested.

VIII. Rejection under 35 U.S.C. § 103

Claims 24 and 38-40 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Lui, taken in combination with U.S. Patent No. 5,817,634 to Meezan ("Meezan"). The Examiner admits that Liu fails to explicitly address diabetes mellitus types 1 and 2, but mistakenly concludes that Meezan can compensate for what Lui lacks. *See* Office Action at page 14. The Examiner alleges that Meezan discloses that diabetes mellitus consists of two subtypes, Type I and II, both of which are "best characterized by hyperglycemia due to an absolute or relative lack of insulin." *Id.* Applicants traverse this rejection for at least the reasons that follow.

To establish a *prima facie* case of obviousness, the prior art reference (or references when combined) must teach or suggest all of the claim limitations. The teaching or suggestion to make the claimed combination must be found in the prior art, and not be based on Applicants' disclosure. *See* M.P.E.P. §§ 2143.01 and 2143.03.

As discussed above, Lui does not disclose, teach or suggest the ability of amylin or amylin agonists to moderate or reduce a postprandial rise in plasma glucose. Meezan does nothing to provide a teaching or suggestion as to the benefits of amylin or amylin agonists. As such, neither Lui nor Meezan, whether taken together or separately, teach or suggest the ability of

amylin or amylin agonists to moderate or reduce a postprandial rise in plasma glucose. There is no suggestion in any of the cited references regarding what the effect of amylin or an amylin agonist would be on postprandial rise in plasma glucose. Whatever else Lui or Meezan might teach or suggest, neither Lui nor Meezan teach or even suggest the benefits of amylin or amylin agonists.

Applicants respectfully submit that the cited references do not render the present claims obvious, since significant limitations of the claims are neither taught nor suggested by the cited references. Withdrawal of this rejection is therefore respectfully requested.

IX. Rejection under Double Patenting

U.S. Patent No. 6,114,304

Claims 24-30 and 38-59 stand provisionally rejected under the judicially created doctrine of obvious-type double patenting as allegedly being unpatentable over claims 1-35 of co-owned U.S. Patent No. 6,114,304 (the '304 patent). Applicants respectfully disagree.[1] However, in order to facilitate prosecution, Applicants are willing to consider submitting a Terminal Disclaimer in the present case with regard to the '304 patent upon an indication of allowable subject matter.

U.S. Patent No. 6,417,164

Claims 24-30, 38, 40-57 and 59 stand provisionally rejected under the judicially created doctrine of obvious-type double patenting as allegedly being unpatentable over claims 1-18 of co-owned U.S. Patent No. 6,417,164 (the '164 patent). Applicants respectfully disagree.[2] However, in order to facilitate prosecution, Applicants are willing to consider submitting a

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1 It is noted that the filing of a Terminal Disclaimer to obviate a rejection based on non-statutory double patenting is not an admission of the propriety of the rejection. *See, e.g., Quad Environmental Technologies Corp. v. Union Sanitary District*, 946 F.2d 870, 20 USPQ2d 1392 (Fed. Cir. 1991) ("filing of a terminal disclaimer simply serves the statutory function of removing the rejection of double patenting, and raises neither a presumption nor estoppel on the merits of the rejection.")

2 *Id.*

Terminal Disclaimer in the present case with regard to the '164 patent upon an indication of allowable subject matter.

CONCLUSION

In view of the above, each of the presently pending claims is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding objection and rejections of the claims, and to pass this application to issue. The Examiner is encouraged to contact the undersigned should any additional information be necessary for allowance.

Respectfully submitted,

Kristan Lansbery

David R. Marsh (Attorney Reg. No. 41,408)
Kristan L. Lansbery (Agent Reg. No. 53,183)

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ARNOLD & PORTER LLP
555 Twelfth Street, NW
Washington, D.C. 20004
(202) 942-5000 telephone
(202) 942-5999 facsimile